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Occult Hepatitis B infection and immunity

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Abstract

Chronic hepatitis B virus (HBV) infection is a major global problem despite the availability of an efficacious vaccine. In Chronic HBV infection, liver cirrhosis and hepatocellular carcinoma (HCC) are associated with considerable morbidity and mortality. The detection of hepatitis B virus surface antigen (HBsAg) in serum remains the mainstay in the diagnosis of Chronic HBV infection and screening for HBV in most developing countries. The majority of individuals positive for HBsAg are also positive for HBV DNA in the serum. Occult HBV infection is characterized by the presence of HBV DNA in the absence of detected HBsAg. Recovery from an acute hepatitis B virus (HBV) infection is associated with loss of HBV DNA from serum, hepatitis Be antigen seroconversion (HBeAg), hepatitis B surface antigen (HBsAg) seroconversion, and normalization of serum aminotransferases. These changes generally imply clearance of virus, but clinical observations have shown that reactivation of HBV infection can occur either spontaneously or after immunosuppression. Recent studies showed that immune response to HBV remains vigorously long after an acute infection. In addition, HBV DNA can be detected by polymerase chain reaction (PCR) assay in serum, liver and peripheral blood mononuclear cells more than a decade after an apparent recovery from HBV infection. These findings suggest that recovery from acute hepatitis B may not result in complete virus elimination but rather the immune system keeps the virus at very low levels. The availability of PCR assays for HBV DNA allows the detection of 10^2 copies /ml compared with 10^6 copies /ml using hybridization assays. Using PCR assays, HBV DNA has been detected in some subjects who are HBsAg negative including those with no serological markers of HBV infection.

Keywords: Chronic hepatitis B virus, hepatitis B virus surface antigen, HBV DNA from serum, hepatitis Be antigen.

Introduction

Hepatitis B virus (HBV) belongs to a family of closely related DNA viruses called the hepadnaviruses and it contains a 3.2-kb partially double-stranded DNA genome with four open reading frames encoding seven proteins (Lee, 1997) .HBV is a major causative agent of hepatocellular carcinoma (HCC) and it remains a major public health problem worldwide (El-serag,

2011; Obeagu and Obeagu, 2017). Up to 400 million people worldwide have hepatitis B surface antigen (HBsAg)-positive chronic viral infection, which is primarily acquired by vertical transmission in high-endemicity countries. However, in individuals with low HBV viral load, HBV may not be detectable by commonly used serological assays based on detection of HBsAg and this unapparent infection makes the true incidence of HBV infection difficult to estimate. Thus, the pathogenic importance of HBV infection may be greater than that presently assumed (Lok and McMahon, 2001).

During the natural history of chronic hepatitis B, seroconversion from HBsAg to anti-HB surface antibody (anti-HBs) is related to the remission of active hepatitis and improvement of liver function and pathological features.

Individuals who have recovered from acute hepatitis B or those who have lost serum HBsAg during their clinical course might carry HBV genomes for several years without presenting any clinical evidence of chronic liver disease (Wong *et al.,* 2011).

Detection of hepatitis B surface antigen (HBsAg) in blood is diagnostic for hepatitis B virus (HBV) infection. In the blood bank, screening for HBsAg is carried out routinely to detect HBV infection. Transmission of HBV infection has been documented from HBsAg-negative, anti-HBc-positive blood and organ donors. Notably, donations from donors in seroconversion stage, from chronic HBV carriers with low circulating HBsAg level as well as from donors infected with some mutant HBV, may not be detected by the currently employed HBsAg assays. Thus among the common blood borne virus infections the risk of transfusion transmitted infection is highest for HBV (Busch, 2004). Use of sensitive molecular assays has led to the detection of potentially infectious HBV DNA in the liver, serum, or both, in individuals without detectable HBsAg in circulation. In a small proportion of individuals, detectable HBV DNA in the serum and/or the liver is observed in the absence of circulating HBsAg (Raimondo *et al.,* 2008).

Occult hepatitis B infection (OBI) is defined by the presence of HBV DNA in the liver tissue of individuals who test negative for HBsAg, regardless of the detection of HBV DNA in serum (Raimondo *et al.,* 2007). Because HBV-DNA detection is the key to diagnosis of occult HBV infection, the type of assay used and its sensitivity must be specified. Occult hepatitis B infection was first reported in the 1980s when hybridization techniques for the detection of HBV DNA became available (Brechot *et al.,* 1985). Prevalence of occult hepatitis B infection has been demonstrated to be associated with the overall prevalence of HBV infection in a given country (i.e., individuals from countries highly endemic for HBV are more likely to develop OBI). Prevalence is higher in seropositive patients, particularly those who are positive for antibody to HB core antigen (anti-HBc), than in seronegative patients who are negative for anti-HBc as well as anti-HBs. Anti-HBc positivity is thus reported to be a surrogate marker for such latent HBV carriers (Jilg *et al.,* 1995). Occult hepatitis B infection is observed in up to 30% of serum samples and 50% of liver biopsies of patients with chronic hepatitis C virus (HCV) infection (Ikeda *et al.,* 2009.

Definition of occult hepatitis b infection (OBI)

Chronic HBV infection is defined by the persistence of serum HBsAg for >6 months. The gold standard for diagnosis of OBI is analysis of HBV-DNA extracts from the liver and blood samples. However, extracted liver samples are only available in a minority of cases therefore; diagnosis of OBI is most often based on analysis of serum samples (Raimondo *et al.,* 2008). In general, OBI is defined by the presence of HBV DNA in the liver tissue of individuals who test negative for HBsAg, regardless of the detection of HBV DNA in the serum.

Highly sensitive commercial assays should be preferred for HBsAg and HBV-DNA testing. When HBV DNA is detectable, its level in the serum is usually low (<200 IU/mL). Occult HBV infection is also reported in the context of other HBV serology markers. Broadly, individuals are classified as being seropositive or seronegative. "Seropositive" subjects are positive for antibodies to hepatitis B core antigen (anti-HBc) and can be further divided into 2 subgroups: with and without

anti-HBs. "Seronegative" subjects are negative for both anti-HBc and anti-HBs. As indicated in the review by (Brechot *et al.,* 2001) the HBV-DNA detection rate is highest in subjects who are anti-HBc positive/anti-HBs negative some of these individuals probably have low-level HBV infection with subdetectable HBsAg. The HBV-DNA detection rate is intermediate in subjects who are positive for both anti- HBc and anti-HBs. These individuals may have recovered from previous infection but may have persistent low levels of HBV. The HBV-DNA detection rate is lowest in seronegative subjects. These individuals have recovered from previous infection but lost all serologic markers of HBV infection. Rarely, they may be infected with HBV mutants that do not express HBV serologic markers.

More than 20% of individuals with OBI have no seropositive markers (Torbenson and Thomas, 2002). In addition, viral replication appears to be regulated by different mechanisms: for patients with ariti-HBc positivity, by a T-cell response of protective memory; whereas anti-HBc-negative patients have no HBV-specific T-cell expansion, indicating that persistent low HBV-DNA infection is insufficient for protective memory to mature.

Pathogenesis of Hepatitis B Virus (HBV) Persistence

Occullt hepatitis B infection (OBI) is mostly due to the indefinitely intrahepatic persistence of the viral genome of wild-type HBV (without any mutations in the precore and core promoter regions) (De La Fuente *et al.,* 2011). Strong suppression of viral replication and gene expression by antiviral cytotoxic T cells is responsible for the very low or undetectable levels of serum HBV DNA in OBI. Conversion of viral genome to a covalently closed circular DNA (cccDNA), which is formed in the nuclei of infected hepatocytes within the first 24 h following virus inoculation and forming of a minichromosome after binding to proteins, is the molecular basis of persistence (Ocana *et al.,* 2011). The stability and long-term persistence of viral cccDNA molecules, together with the long half-life of hepatocytes, imply that HBV infection, once it has occurred, may possibly continue for life .

The cccDNA correlation with serum HBV DNA is poor, among HBeAg-negative individuals (Levrero *et al.,* 2009)

Clinical utility of intrahepatic cccDNA assay is very limited due to the invasiveness of liver biopsy but a more realistic approach is the quantitative measurement of serum HBsAg, which correlates well with intrahepatic cccDNA levels in both HBeAg-positive and -negative patients (Levrero *et al.,* 2009). cccDNA is the main template for the transcription of viral mRNAs and has been shown to persist in hepatocytes even with successful cellular and humoral control of the infection indicated by HBsAg/anti-HBs seroconversion. With the impairment of host defense systems, cccDNA can evade host immunity and actively replicate again.

Mechanisms potentially involved in Hepatitis B virus (HBV) inhibition and occult hepatitis b infection (obi) status induction

Host factors

Much evidence indicates that host factors are strongly implicated in the induction and maintenance of the occult status of HBV infection. Further proof is provided by a recent in vitro study showing that replication, transcription, and protein synthesis abilities of occult viral isolates can be fully restored once the viruses are taken out from the host's liver microenvironment (Pollicino *et al.,* 2007).

Immunological factors

Numerous clinical studies have clearly demonstrated since the 70s that all the conditions inducing immunosuppression (i.e., hematologic malignancies, chemo- or immunotherapies, etc.) may provoke the reactivation of OBI with the reappearance of the typical serological profile of overt active, infection (Torbenson and Thomas , 2002). This involvement is also confirmed by the data showing that a long-lasting memory CD4 and CDS cell- responses against HBV antigens are still detectable several years after recovery from acute hepatitis B possibly because during the occult phase of the infection, HBV is still

able to synthesize minute amounts of antigens, which are umceteciable by available technical approaches but are sufficient enough to maintain an HBV-specific T cell response (Penna *et al.,* 1996). Indeec, besides HBV cccDNA molecules, all viral transcripts have been detected in the liver of occult-infected individuals (Wong *et al.,* 2011) and real-time PCR quantification has revealed small but still quantifiable amounts of intrahepatic HBV mRNA in these subjects. Therefore, clinical recovery from HBV infection not only implies the lack of complete clearance, of the virus but also reflects the ability of the immune system to keep under tight control leftover viruses in the liver after clinical resolution of disease. .

Viral factors

Since the lack of detectable HBsAg in serum is a characterizing feature of OBI, considerable interest has been focused on mutations in the surface gene and its regulatory regions. Thus, besides mutation clustering in key immunodominant regions of the surface protein able to decrease the immune recognition of the virus, deletions in the preSl region impairing viral packaging, structural alteration in genomic regulatory regions leading to a strong reduction of HBsAg expression, and mutations affecting posttrarislational production of HBV proteins have been described (El *et al.,* 2010).

Coinfection

HBV activity might be impaired by other infectious agents hi cases with coinfection. In particular, Hepatitis C Virus (HCV) has been suspected to strongly suppress HBV replication up to the point where it determines OBI development in coinfected individuals. In fact, a number of in vitro studies had clearly demonstrated that the HCV "core" protein strongly inhibits HBV replication (Raimondo *et al.,* 2005) and OBI shows the highest prevalence precisely in HCV-infected patients (Torbenson and Thomas ,2002). Even individuals positive for human immunodeficiency virus (HIV) frequently show either overt or occult HBV coinfection, but there is no evidence of possible direct effects of HIV on HBV activity. Finally, other infectious agents might also potentially inhibit HBV and it has been shown that schistosoma mansoni is capable of strongly suppressing HBV replication in a transgenic mice model (McClary *et al.,* 2000).

Mutations and Deletions in the HBV Genome

Sequence variation in HBV genomes, including (i) mutations in the "a" determinant of HBsAg, (ii) treatment-associated mutations, (m) splicing, and (iv) mutations in the pre-S region have been linked to occult HBV infection

Epigenetic Changes

Methylation. In the human genome, regions rich in CpG dinucleotides are referred to as CpG islands. Methylation of cytosines in CpG dinucleotides within CpG islands in gene promoters leads to gene silencing. Methylation is a key, mechanism for regulation of transcriptional activity. Methylation of HBV DNA represents a novel epigenetic mechanism that impairs HBV proteins, HBV replication, and HBV virion production, leading to occult HBV infection. Nearly 2 decades ago it was demonstrated that HBV DNA integrated into the host genome is methylated. Methylation of HBV DNA encoding the HBV core protein leads to loss of HBV core protein in PLC/PRF/5, a human hepatoma cell line with integrated HBV DNA sequences (Miller and Robinson, 1983). It was generally accepted that only integrated HBV DNA sequences are methylated. However, the observation of chromatin-like minichromosomes during replication prompted the search for CpG islands in episomal DNA, and three were recently identified (Vivekanandan *et al.,* 2008). Episomal HBV DNA from human liver tissue and from cell culture can be methylated. Of note, methylation of CpG island 2 in the HBV genome is frequently detected in occult HBV infection (Vivekanandan *et al.,* 2008). HBV cccDNA is frequently methylated in human liver tissues (Vivekanandan *et al.,* 2009). Transfection of *in* vz/ro-methylated HBV DNA constructs into hepatocyte cell lines was associated with a _90% decrease in secreted HBsAg. In addition, HBeAg and HBcAg expression was markedly reduced by methylation of HBV, clearly demonstrating the

role of CpG islands in regulating HBV gene expression (Vivekanandan *et al.,* 2009). HBV replication in cell culture induced the expression of DNA methyltransferases (DNMTs), enzymes vital for DNA methylation. The HBV-induced DNMTs could methylate HBV DNA, resulting" in the inhibition of HBV transcription and HBV replication (Vivekanandan *et al.,* 2010). Hypermethylated HBV DNA sequences are frequently detected in Hepatocellular carcinoma (HCC) patients with occult HBV infection. Methylation of cccDNA is associated with low serum HBV DNA levels and decreased virion production in patients with liver cirrhosis (Kim, 2011). The association between HBeAg and high virus loads is well known.

Host Immune Responses and Occult Hepatitis B Infection (OBI)

Virus-host interactions play a crucial role in determining the outcome of hepatitis B virus infection. Host immune responses are involved in viral clearance, viral persistence, and immunopathogenesis of HBV infection. Interestingly, several host immune response-related mechanisms, such as apoptosis, cytolytic and noncytolytic T-cell responses, and vitamin D receptor (VDR) polymorphisms, have been linked to modulation of HBV replication and HBV protein synthesis.

However, only a few studies have implicated modulation of the host immune response as a stand-alone mechanism leading to occult hepatitis B virus infection. (Martin, 2009) compared the serum cytokine expression profiles in HIV-infected patients with chronic HBV infection or with occu.lt HBV infection. Lower soluble Fas (sFas) levels were detected in occult HBV infection than in chronic HBV infection (P=0.01) (Martin, 2009).

The Fas expression system is known to modulate apoptosis of infected hepatocytes and also plays a key role in the removal of aged hepatocytes and maintenance of normal liver homeostasis (Hayashi and Mita, 1999). (Martin ,2009) argued that their finding of lower sFas levels in occult HBV infection indicates decreased apoptotic inhibition in occult HBV infection and could be one of the mechanisms for clearance of HBsAg and down regulating HBV replication in occult HBV infection (Martin, 2009).
It has been suggested that reduced expression of CXCL12, a chemokine that modulates apoptosis, may play a role in occult HBV infection. Additional studies are required to evaluate the role of apoptosis in modulating the course of HBV infection. Differences in the HBV-specific cell-mediated immune response have been described in occult HBV infection. Anti-HBc positive occult HBV patients had T-cell responses concurrent with protective memory, while anti-HBc-negative occult HBV patients had inadequacies in maturation of protective memory (Zerbini, 2008). The presence of HBV-specific CD8_ T cells in occult HBV infection without anti-HBc was demonstrated by staining with class I major histocompatibility complex tetramers (Zerbini, 2008).

Prevalence of Occult Hepatitis B Virus Infection (OBI)

Considering the HBV life cycle with a long-lasting persistence of viral genomes in most infected patients independently of HBsAg status, OBI is expected to be a worldwide diffused entity, which prevalence is higher in populations at high risk of parenterally transmitted infections and generally dependent on the level of HBV endemicity in the different geographic areas. The prevalence of occult HBV infection also depends on the population studied, being more common in patients with chronic liver disease and less common amoung healthy blood organ donors.

In addition, there is considerable evidence indicating that OBI is highly prevalent also in individuals with Chronic liver disease (CLD) and, in particular, in HCV chronically infected patients (Raimondo *et al.,* 2007) In fact, HBV DNA is detectable in about one-third of HBsAg-negativ.e HCV carriers in the Mediterranean Basin and in more than 50 % in Far East Asian countries (Torbenson and Thomas, 2002). Of note, recent studies conducted in the USA on patients of Caucasian origin undergoing liver transplantation for HCV-related cirrhosis showed that 50 % of these individuals were OBI-positive. These data are particularly surprising and relevant taking into account that HBV prevalence in the Caucasian

American population is one of the lowest in the world (Shouval, 2008). OBI has been less investigated in patients with HCV-negative cryptogenic liver disease (CLD). Its prevalence has been reported to range between 20 % and 30 % in subjects with cryptogenic liver disease (Wong *et al.*, 2011). In one study, 12.2 % of patients with chronic hepatitis related to autoimmune disorders proved OBI-positive when serum samples were tested, although this prevalence appeared to significantly increase when viral DNA was also assayed on liver extracts of a number of those patients.

Populations at high risk of parenterally transmitted infections have been widely investigated for occult HBV. A high prevalence has been reported in intravenous drug addicts in Baltimore (45 %) (Torbension *et al.*, 2004) and in hemophiliacs in Japan (51 %) (Toyoda *et al.*, 2004). Of note, the highest prevalence was found when the most sensitive techniques for OBI detection were used and when longitudinally collected multiple patient sera were tested. However, only one study evaluated the presence of HBV sequences at intrahepatic level, showing that 41 % of HTvYHCV coinfected Italian patients also carried OBI. OBI has been extensively explored in blood donors where it appears to occur quite rarely in the western world, whereas it is frequently detected in developing countries (Raimondo *et al.*, 2007).

On the contrary, OBI has been much less investigated in the general population so far. In a study evaluating HBsAg-negative residents of a Canadian Inuit community, HBV DNA was detected in 18 % of anti-HBc positive subjects and hi 8 % of HBV seronegative individuals, respectively, whereas occult HBV genomes were found in 16 % of Korean HBV/HCV-negative healthy subjects with normal transaminase values and in 15.3 % of healthy hematopoietic stem cell donors from Hong Kong (Kim *et al.*, 2007).

We recently investigated the presence of HBV DNA at intrahepatic level in 98 liver disease-free HBsAg-negative Italian individuals who underwent liver resection or needle liver biopsy during abdominal surgery: 16 of them (16 %) were OBI positive, most having circulating anti-HBV antibodies (Raimondo *et al.*, 2008).

Risk of Occult Hepatitis B Virus Infection (OBI) transmission

Blood transfusion

It is well established that carriers of occult infection may be a source of HBV transmission in the case of blood transfusion with the consequent development of a typical type B hepatitis in the recipients. Schematically, three conditions may be responsible for the transfusion transmission of HBV:

1. The donor is in the window period (the HBsAg-negative, viremic, early acute phase of HBV infection). It accounts for a minority of OBI-positive blood donors (Allian and Cox, 2011). In the case of window period donation, HBsAg or anti-HBc screening would not be able to identify an OBI which has prompted the implementation of HBV DNA NAT screening inmany countries.

2. The donor is a typical "OBI carrier" with a wild-type virus which replication activity and gene expression are suppressed. This point is important and intriguing, and it should be taken into account that OBI infection is characterized by periods of transient HBV viremia alternating with periods in which the viral DNA is undetectable in the serum (Chemin *et al.*, 2009). Thus, an occult HBV-infected individual may have a profile of blood infectivity fluctuating over time. However, one important point is the real ability of the very low amount of serum HBV DNA usually present in OBI carriers to generate acute hepatitis B in the recipient. It seems that HBV DNA-positive donors with anti-HBc as the only serological marker are more infectious than those carrying anti-HBs (Allian and Cox, 2011). Although the possibility of inducing acute hepatitis is likely dependent on the viral load, the amount of plasma transfused the immunocompetence of the recipient, and the HBV serological status (presence/absence of anti-HBc and/or anti-HBs) in both donor and recipient. Nevertheless, it should be considered that the lack of acute hepatitis development does not exclude HBV transmission and infection of the

recipient who, in turn", might theoretically become occult HBV-infected.

3. The donor is infected with variant HBV strains (S-escape mutants) that are replication-competent but produce abnormal surface proteins that are not recognized by the commercially available HBsAg detection kits. This condition appears to be a major cause of the residual cases of HBV transmission by blood transfusion. In this context, the use of multivalent anti-HBs antibodies in the HBsAg detection kits has been recently recommended by an expert panel for the identification of blood donors infected by HBsAg escape mutants (Raimondo *et al.*, 2008), even if this strategy does not definitely solve the problem of post-transfusion HBV infection, especially in geographic areas where HBV infection is highly endemic and the viral genomic variability is potentially the highest. The introduction of Nucleic Acid Testing (NAT) for HBV was intended to identify all blood donors with circulating HBV DNA independently of each of the above reported conditions. Actually, NAT for HBV has revealed that a small part of HBsAg-negative blood donors worldwide have detectable amount of HBV DNA in the serum.

Clinical Impact of OBI

OBI- is a complex entity that comprises many conditions and different situations (Liedo *et al..*, 2011). OBI may be involved in several clinical contexts as follows: reactivation of the infection and consequent development of the HBV- related liver disease; transmission of the "occult" virus mainly through blood transfusion and orthotopic liver transplantation (OLT) with consequent hepatitis B in the recipient; the effect on occurrence and progression of the Chronic liver disease (CLD); and the role in hepatocarcinogenesis (Raimondo *et al.*, 2013).

In OBI, HBV reactivation can be induced by treatment of cancers and autoimmune diseases (Matsumoto *et al.*, 2010). Development of a classic hepatitis B that often has a severe clinical course is possible if suppression of viral replication discontinued as in several conditions including HIV infection, hematological malignancies, patients undergoing chemotherapy, transplantation (bone marrow, liver, or kidney), and treatment with, potent immunosuppressive drugs like rituximab (anti-CD20), alemtuzumab (anti-CD52), or uiflixirnab (antitumor necrosis factor) (Liedo *et al.*, 2011). Different reports suggest that OBI could be responsible for the acceleration of chronic hepatitis C virus (HCV) progression and interfere with treatment response (Levast *et al.*, 2010).OBI is found in up to 30% of serum samples and 50% of liver biopsies of patients with chronic hepatitis C and 20% and 30% in subjects with cryptogenic liver disease . OBI may favor or accelerate the progression toward cirrhosis, associated with the most severe forms of liver disease in HCV-infected patients. Preliminary evidence suggests a possible involvement in faster progression of posttransplant liver disease in HCV-positive patients with OBI in donor or recipient (Toniutto *et al.*, 2009).

HCV has been suspected to strongly suppress HBV replication up to the point where it determines OBI development in coinfected individuals. OBI is the major cause of post transfusion hepatitis B in western countries and in countries like India and Taiwan, with higher risk of transmission than for HCV or HIV (Regan *et al.*, 2000).

Recently, a meta-analysis showed an increased risk of HCC associated with OBI with an odds ratio of 2.9 (95% CI: 1.6-4.1) in retrospective and prospective studies. It is generally believed that OBI maintains most of the pro-oncogenic properties and can contribute to hepatocellular transformation through the same direct and indirect mechanisms that subtend HCC development in overt HBV infection (Raimondo *et al.*, 2013).

OBI must be investigated in the following clinical situations: (1) solid organ, hematopoietic stem cell transplantation, and blood transfusion; (2) cryptogenic chronic hepatitis and hepatocellular carcinoma unrelated to HCV, atypical alcoholic hepatitis; (3) immunosuppresive therapy; (4) haemodialysis; (5) chronic hepatitis C especially those with flare in liver enzymes . Consequently, it is important to detect high-risk groups for occult HBV infection (Ceneli *et al.*, 2010).Clinicians must be aware of these clinical events and establish a

standard strategy to prevent HBV reactivation (Larrubia *et al*., 2011).

Occullt Hepatitis B infection (obi) reactivation

Definition of HBV reactivation among patients with OBI has been reported as the reappearance of HBsAg or HBV-DNA in the blood (Hui *et al.,* 2006). With resolved hepatitis, HBV reactivation usually begins later than 4 months. Consequently, HBV reactivation in irnrnunocompromised patients has recently been the focus not only of many studies but also of meetings, reviews, and position papers (Lalazar *et al.,* 2007).

Thus, the strong suppression of viral replication and gene expression typical of the occult HBV status may be discontinued in patients under conditions of immunosuppression, who may consequently have a reactivation of the viral replication because of the drop in immunological control. Of note, however, recent reports indicate that also the use of historic deacetylase inhibitors may be associated with OBI reactivation (Grewal *et aL,* 2007), confirming the involvement of epigenetic mechanisms in the control of HBV activities and, consequently, modifications of viral cccDNA minichromosome structure and dynamics as possible causes of viral reactivation.

One main question is how frequent the viral reactivation in OBI patients is. Surely, it occurs more rarely than in HBsAg-positive cases, and it likely varies depending on different clinical settings and therapeutic treatments, hematological malignancies, hematopoietic stem cell transplantation, and treatments including rituximab conditions being at high risk (Yeo *et al.,* 2009).

In this context, we would like to stress that OBI reactivation is usually diagnosed when it is followed by the occurrence of acute hepatitis. However, there is clear evidence that OBI individuals may frequently change their HBV serological profile if immunocompromised: in fact, anti-HBs positive individuals may lose this antibody during rmmunosuppressive therapy and two distinct studies have revealed that HBsAg re-seroconversion often occurs in subjects undergoing hematopoietic stem cell transplantation, although only a minority of these cases develop clinically typical acute hepatitis (Vigano *et al.,* 2011). Consequently, one might speculate that OBI reactivation is a quite frequent occurrence in itself, but it is rarely followed by a clinically acute event, thus its recognition and diagnosis might be missed in many cases. Because of the low risk of HBV reactivation in patients with resolved infection with anti-HBs titer >10IU/L, close follow up of LFTs was thought to be sufficient in immunosuppressive treatment groups; although serial HBV-DNA monitoring is a reasonable strategy.

Diagnosis of occult Hepatitis B infection

The gold standard for diagnosis of OBI became possible by highly sensitive and specific molecular biology techniques like HBV nucleic acid amplification testing (NAT), a PCR technique with detection limits of <10 copies HBV DNA per reaction (Raimondo *et al.,* 2008). Samples for analysis include specimens from the liver and blood but diagnosis of OBI most commonly is based on the analysis of serum samples, because liver specimens are only available in a minority of cases and standardized assays for use hi liver tissue are not yet available (Raimondo *et al.,* 2008). If highly sensitive HBV DNA testing is not feasible, anti-HBc should be used as a less than ideal surrogate marker for identifying potential seropositive OBI individuals in cases of blood, tissue, or organ donation, and when immune suppressive therapy has to be administered (Gerlich *et al.,* 2007).

In this context, it has to be stressed that not all anti-HBc-positive individuals are found to be HBV DNA positive and that anti-HBc tests may provide false positive results (Cornanor and Holland, 2006). OBI is more often detected in patients positive for and- HBc but negative for anti-HBs, presumably ..because these patients lack the neutralizing effect of anti-HBs (Brechot *et aL,* 2001). Most frequently, seropositive occult HBV infection follows resolution of acute hepatitis and continues indefinitely after clearance of HBsAg and biochemical improvement in liver function; it can also occur after years of chronic HBsAg-positive infection (Huo *et al.,* 1998).

Preventive Measure

It would probably be best to administer preventive treatment for HBV reactivation as this would inhibit the development of hepatitis and mortality with the aim of inhibiting the replication of HBV (Manzano and Gastellanefc-Tortajade, 2011). Antiviral prophylaxis should be continued for > 6 months after stopping chemotherapy and for certain immunosuppressive therapies, such as riMximab; it may be better to maintain the prophylaxis until restoratiom of host immunity. All patients who receive chemotherapy and immunotherapy should be tested for serologic markers of HBV infection, including HBsAg, anti-HBc, and anti-HBs before any chemotherapy or immunosuppressive therapy, and monitored for several months or years after stopping treatment because antibody titers may be reduced by the immunosuppressive therapy (Larrubia *et al.*, 2011).
Antiviral drugs should be initiated to OBI, especially in the absence of anti-HBs which are potentially at greater risk for HBV reactivation prior to chemotherapy and continued for >6 months after stopping immunosuppressive treatment (Hollinger and Sood, 2010).The appearances of HBsAg and HBV DNA in up to 50% of anti-HBc positive patients undergoing bone marrow transplantation have been reported. Prophylaxis with antiviral agents prevents reactivation of OBI in most of transplant cases with HBsAg-negarive and anti-HBc-positive donors and it is not known if prior hepatitis B immunization with an optimal anti-HBs respense can modulate or abort the infection (Larrubia *et al.*, 2011). Serial HBV-DNA monitoring (monthly during and after chemotherapy for at least 1 year) is a reasonable strategy recommended by the latest Japanese guidelines; in this regard multicenter clinical trial in Japan is now continued. Although in blood transfusion the risk of transmission is insignificant when anti-HBs is present in the blood, caution is recommended when immunodeficient patients receive anti-HBc-positive and anti-HBs-positive donations (Lamibia *et al.*, 2011).

The use of HBV-DNA NAT and multivalent anti-HBs antibodies in the HBsAg assays is recommended for detection of true and false OBI, respectively, and to minimize the risk of HBV transmission through transfusion .(Larrubia *et al.*, 2011). This is important because almost 50% of transfused blood in Western Europe is given to immunodeiicient patients (Candotti and Allian, 2009).

Conclusion

For detection of OBI -HBV DNA nucleic acid testing should be implemented even if anti-HBc and anti-HBs were negative especially in endemic area and in suspected high-risk cases (populations at high risk of parenterally transmitted infections) with probable previous exposure before blood and organ donation, transplantation, and chemotherapy and in hemodialysis and cryptogenic chronic hepatitis. The use of multivalent anti-HBs antibodies in the HBsAg detection kits is strongly recommended. All patients receiving chemo- and irnmunotherapy should be tested at least once for anti-HBc antibodies before starting therapy and monitored periodically for ALT elevations.

If ALT elevations occurred, the diagnosis of HBV reactivation must be established with further testing before initiation of antiviral prophylaxis. Optimal duration of prophylaxis in different risk populations should be clarified or even individualized in the future. OBI is a complex disease entity comprising different situations. The definition of OBI should be based on high-sensitivity HBsAg and HBV-DNA testing. The cumulative evidence has revealed its possible implication in various clinical contexts. The oncogenic potential of OBI has become progressively evident.OBI may exert oncogenic activity through direct and indirect mechanisms, and it can affect liver disease progression and hepatocarcinogenesis in patients with other viral causes, particularly HCV, as well as in those with hepatitis-unrelated liver disease. OBI may be a potential risk factor for development of other cancers.

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